The Counteracting Effect of *p*-Hydroxybenzyl Alcohol on the Inhibitory Avoidance Response in Rats: Role of the Central and Peripheral Catecholaminergic Systems

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ABSTRACT

The effect of *p*-hydroxybenzyl alcohol (HBA) on apomorphine (APO)-induced amnesia and the role of the central and peripheral catecholaminergic systems on the counteracting effects of HBA were investigated in an inhibitory avoidance model in rats. It was observed that HBA at doses of 1, 5 and 25 mg/kg significantly attenuated APO-induced impairment. Piracetam at 100 mg/kg also attenuated APO-induced impairment. The counteracting effect of HBA on the APO-induced impairment was significantly antagonized by a D_1-selective agonist, SKF 38393, but was potentiated by the D_1 antagonist, R-(+)-SCH 23390. The counteracting effect brought about by HBA on APO-induced impairment was significantly potentiated by a selective D_2 antagonist, (-)-sulpiride. Intravenous 6-hydroxydopamine did not impair the inhibitory avoidance response, but blocked the counteracting effect of HBA on the APO-induced impairment. Finally, HBA counteracted the 6-OHDA (i.c.v.)-induced impairment of the inhibitory avoidance response.

In conclusion, the counteracting effects of HBA on the APO-induced impairment of the inhibitory avoidance response might be related to modulation of both peripheral and central catecholaminergic neuronal activities via the α_1-receptor and the postsynaptic D_1 and D_2 receptors.

Key words: ***p*-Hydroxybenzyl alcohol; Apomorphine; Inhibitory avoidance; Piracetam; Catecholaminergic systems; Amnesia.**

INTRODUCTION

p-Hydroxybenzyl alcohol (HBA) is a phenolic compound that is an active constituent of

the rhizome of *Gastrodia elata* BLUME (Orchidaceae).[1] In our previous studies, HBA attenuated drug-induced memory impairment of inhibitory avoidance tasks.[2-3] The attenuating mechanisms of the memory processes might be related to dopaminergic (DA) and serotonergic activities.[4] We also demonstrated that the attenuating effect of HBA on drug-induced memory impairment was due to decreased serotonergic neuronal activity via 5-HT_{1A}, 5-HT_2 and α_1-adrenergic receptors.[3,5] However, the role of dopaminergic receptors on the promoting effects of *p*-hydroxybenzyl alcohol in memory processes has never been investigated.

Learning acquisition represents the experience-dependent modification of enduring internal representations. It involves the activation, by neurotransmitters such as acetylcholine, dopamine and serotonin, of receptor-linked enzymes responsible for the synthesis of intercellular messengers.[6-7] Much evidence suggests that DA neurons participate in learning and memory in humans and animals.[8-9] Recent studies show a consistent trend in which the central DA system plays an inhibitory role in avoidance and aversive conditioning tasks.[9] In fact, DA antagonists facilitated learning acquisition.[10-11] while the DA agonist apomorphine (APO), when administered before training, impaired learning acquisition in rodents.[12] Furthermore, two main types of DA receptor have been identified and termed D_1 and D_2 receptors.[13] D_1 and D_2 receptors also play a modulatory role in learning and memory. Recent studies found that D_1 agonists impaired performance in various experimental tasks, and D_2 agonists impaired the performance in inhibitory avoidance tasks.[10-11,14-15] Secondly, peripheral or central catecholaminergic systems also participate in learning and memory[8,16.] The peripheral catecholaminergic system plays a modulatory role in learning and memory.[8,16] The effects of some cognitive enhancers were blocked by peripheral antagonist or intravenous 6-hydroxydopamine (6-OHDA).[17] The central catecholaminergic system plays an important role in learning and memory.[8,16,18] Intracisternal 6-OHDA impaired cognitive function.[19]

In the present study, we investigated whether HBA attenuates APO-induced impairment of learning acquisition in comparison with piracetam[20] as a positive control. To demonstrate the action mechanism of HBA, we further examined HBA combined with the D_1 agonist (±)-SKF 38393 and antagonist R-(+)-SCH 23390 as well as with the D_2 agonist quinpirole and antagonist sulpiride. We also examined combination of HBA with the catecholaminergic neurotoxin 6-hydroxydopamine administered either intravenously or intracisternally.

MATERIALS AND METHODS

Animals

Male Sprague-Dawley rats, weighing 200-250 g, were housed in groups of six with free access to food and water in a regulated environment (23 ± 1°C), wherein a 12 hr light-dark cycle (8:00 to 20:00, light) was maintained. The number of subjects in each group was 12 to 18 as

depicted in the figures.

Inhibitory Avoidance Task

Rats were trained in a step-through inhibitory avoidance task. The apparatus consisted of two compartments having a steel-rod grid floor (36 parallel steel rods, 0.3 cm in diameter set 1.5 cm apart). One of the compartments (48 × 20 × 30 cm) was equipped with a 20W lamp located centrally at a height of 30 cm, and the other was a dark compartment of the same size, connected through a guillotine door (5 × 5 cm). The dark room was used during the experimental sessions that were conducted between 09:00 and 17:00. During the training trial, the guillotine door connecting the light and dark compartment was kept closed. After each rat was placed in the light compartment with its back to the guillotine door, the door was opened and simultaneously the time (step-through latency, STL) taken by the rat to enter the dark compartment was measured with a stopwatch. Once the rat entered the dark compartment, the door was closed. An inescapable scrambled footshock (1 mA for 2 s) was then delivered through the grid floor. The rat was removed from the dark compartment 5 s after administering the shock. The rat was then put back into its home cage until the retention trial, which was carried out twenty-four hours later. The rat was once again placed in the light compartment and as in the case of the training trial, the guillotine door was opened and the step-through latency was recorded and used as a measure of retention.[5] An upper cut-off time of 300 sec was set.

In the first series of experiments, APO (1.0 mg/kg, s.c.) was administered 20 min before the training trial.[12] HBA (0.5, 1, 5 and 25 mg/kg, p.o.) was administered to APO-treated rats 1 h before the training trial.[2-4] Piracetam (50, 100 and 300 mg/kg, p.o.) was also administered to APO-treated rats 1 h before the training trial.

In the second series of experiments, HBA (1 mg/kg, p.o.) was administered to APO-treated rats 1 h before the training or retention trial. (±)-SKF 38393 (10 mg/kg, i.p.) and quinpirole (QUIN, 0.01 mg/kg, i.p.) were given 20 min before the training trial.[14] R-(+)-SCH 23390 (0.1 mg/kg, i.p.) was given 30 min before the training trial.[10] Sulpiride (SUL, 40 mg/kg, i.p.) was given 60 min before the training trial.[10]

In the third series of experiments, 6-OHDA (5 and 25 mg/kg, i.v.) was administered 24 h before the training trial.[17] HBA (1 and 5 mg/kg, p.o.) was administered to 6-OHDA-treated rats 1 h before the training trial.

In the fourth series of experiments, 6-OHDA (250 μg/ 20 μL, i.c.v.) was administered 14 days before the training trial.[19] HBA (1 and 5 mg/kg, p.o.) was administered to 6-OHDA-treated rats 1 hr before the training trial.

Motor Activity in Non-shocked Rats

To evaluate the effect of various drug combinations on motor activity in the inhibitory

avoidance task, the same experimental steps were followed with the exception that rats were not subjected to inescapable footshock during the training period. Twenty-four hours later, the retention trial was carried out and the step-through latency was recorded.[5] The rats were given 1 mg/kg APO in combination with the above mentioned drugs.

Drugs

p-Hydroxybenzyl alcohol (HBA), piracetam (Sigma), apomorphine (APO; Sigma), R-(+)-SCH 23390, (±)-SKF 38393 and quinpirole (QUIN) were all dissolved in 0.9 % saline. 6-Hydroxydopamine (6-OHDA; Sigma) was dissolved in 0.9 % saline containing 0.5 % ascorbic acid. Sulpiride (SUL) was dissolved in distilled water containing a little lactic acid and sodium bicarbonate was added to adjust the pH value to 4.

Statistical Analysis

All data obtained during the inhibitory avoidance task was expressed in terms of medians and interquartile ranges and further analyzed by using a Kruskal-Wallis non-parametric one-way analysis of variance, followed by Mann-Whitney's *U*-test. In addition, the data collected during motor activity was analyzed using a one-way analysis of variance, followed by Scheff's multiple range test. The criterion for statistical significance was $P < 0.05$ in all the above statistical evaluations.

RESULTS

Effects of HBA and Piracetam on APO-Induced Avoidance Impairment

It was observed that APO (1 mg/kg, s.c.) administered 20 min before the training trial remarkably shortened the step-through latency period. As shown in Fig. 1, APO-induced shortening of the step-through latency period was reversed by 1-25 mg/kg HBA administered 1h before the training trial. On the other hand, a much higher dose of piracetam (100 mg/kg) was required to significantly counteract the APO-induced shortening of the step-through latency period (Fig. 1).

Effects of DA Agonists and Antagonists on the Counteracting Effect of HBA on the APO-Induced Avoidance Impairment

The D_1 selective agonist (±)-SKF 38393 (10 mg/kg), which did not shorten the step-through latency period in the retention trial itself, attenuated the HBA recovery of APO-induced shortening of step-through latency (Fig. 2(A)). R-(+)-SCH 23390 (0.1 mg/kg), a D_1 selective antagonist, which did not have a significant anti-amnestic effect by itself, potentiated the HBA recovery of APO-induced shortening of step-through latency (Fig. 2(B)). A D_2

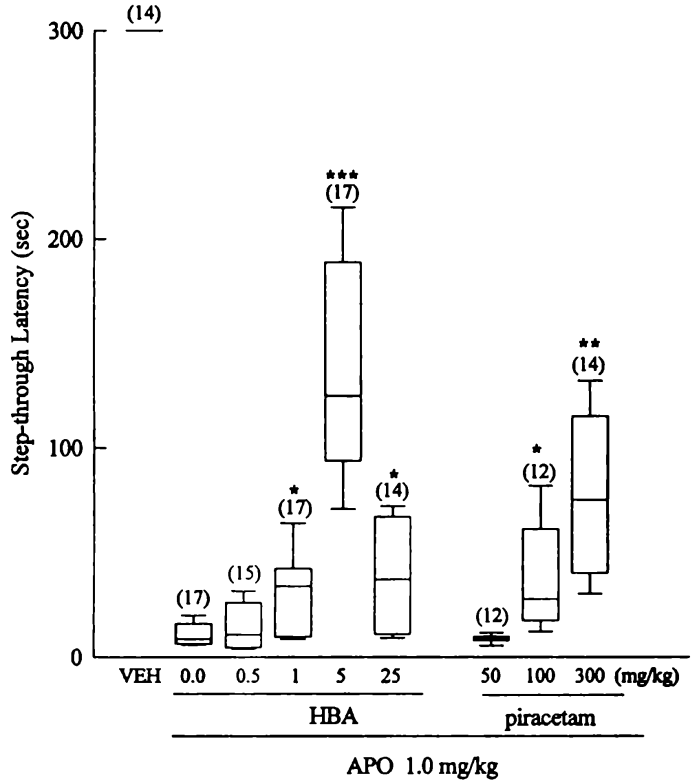

Fig. 1. Effect of *p*-hydroxybenzyl alcohol (HBA) on the APO-induced impairment of avoidance in rats. Each column represents the medians and range inside the 5th and 95th percentiles. * P < 0.05 , ** P < 0.01, *** P < 0.001 compared with APO.

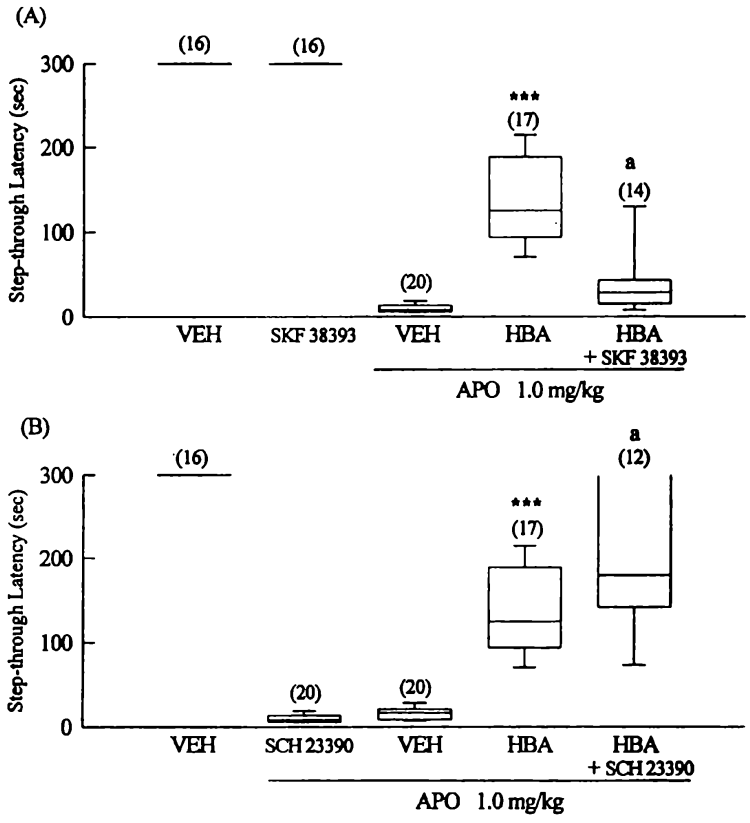

Fig. 2. Effect of SKF 38393 (panel A) and SCH 23390 (panel B) on *p*-hydroxybenzyl alcohol (HBA, 5 mg/kg)-induced recovery from APO-induced impairment of avoidance in rats. Each column represents the median and range inside the 5th and 95th percentiles. *** P < 0.001 compared with APO. a P < 0.05 compared with HBA in combination with APO.

selective agonist quinpirole (0.01 mg/kg), which did not shorten the step-through latency, attenuated the HBA recovery from APO-induced shortening of step-through latency (Fig. 3(A)). (-)-Sulpiride (40 mg/kg), a selective D_2 antagonist, which did not have a significant anti-amnestic effect on its own, potentiated HBA recovery from APO-induced shortening of step-through latency (Fig. 3(B)).

Effects of Catecholaminergic Neurotoxin on the Counteracting Effect of HBA on APO-Induced Avoidance Impairment

Intravenously administration of 5 but not 25 mg/kg 6-OHDA, 1 day before the training trial remarkably shortened the step-through latency period. Intravenous 6-OHDA at 25 mg/kg, which did not have a significa ant anti-amnestic effect on its own, blocked HBA recovery of APO-induced shortening of step-through latency (Fig. 4). 6-OHDA (250 μg/20 μL) administered intracisternally 14 day before training remarkably shortened the step-through latency period. HBA (1 and 5 mg/kg) administered 1 h before the training trial attenuated the 6-OHDA-induced learning performance impairment (Fig. 5).

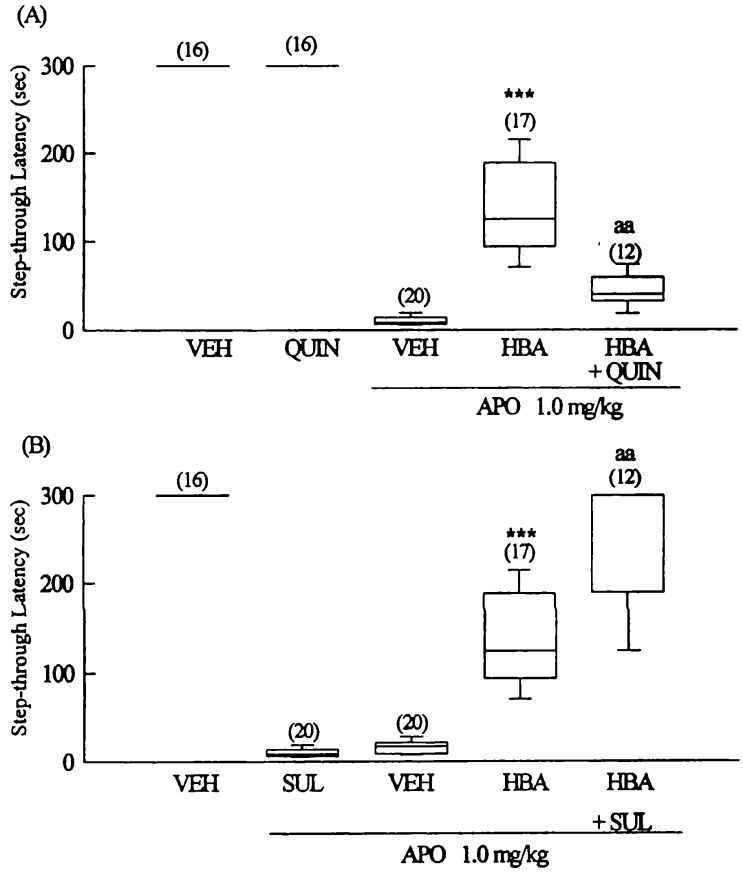

Fig. 3. Effect of quinpirole (QUIN, panel A) and sulpiride (SUL, panel B) on *p*-hydroxybenzyl alcohol (HBA, 5 mg/kg)-induced recovery from APO-induced impairment of avoidance in rats. Each column represents the median and range inside the 5th and 95th percentiles. *** $P < 0.001$ compared with APO. aa $P < 0.01$ compared with HBA in combination with APO.

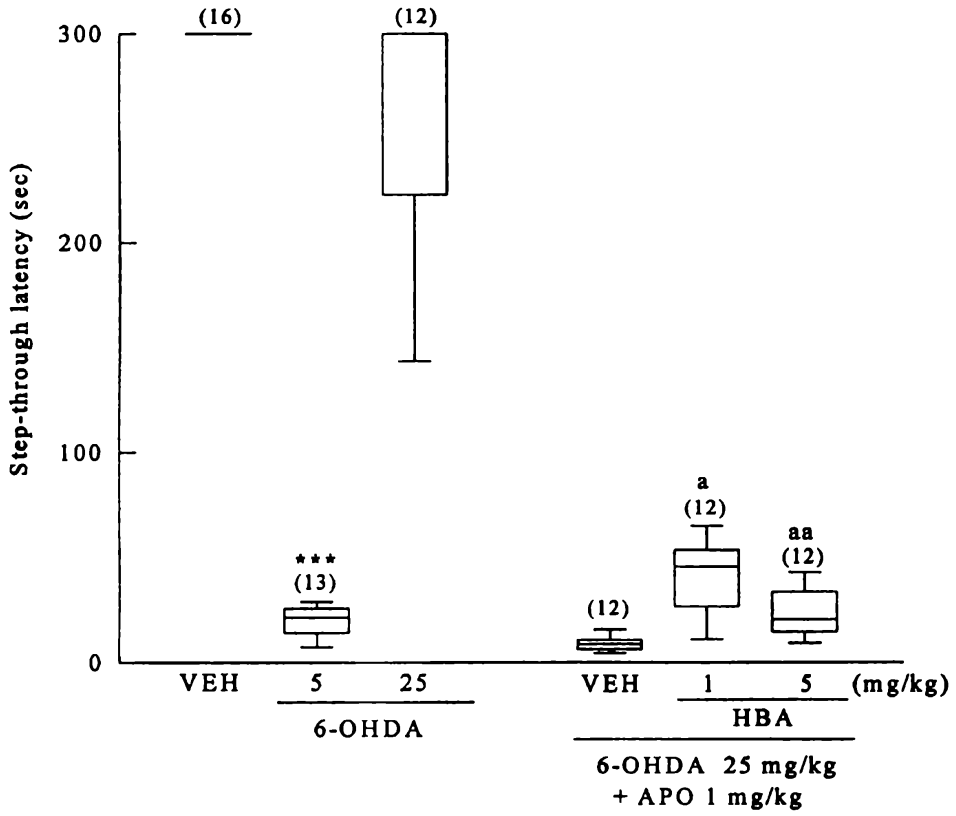

Fig. 4. Effect of6-hydroxydopamine (6-0HDA, i.v.) on *p*-hydroxybenzyl alcohol (HBA)- induced recovery from apomorphine (APO) -induced impairment of avoidance in rats. Each column represents the median and range inside the 5th and 95th percentiles. *** $P < 0.01$ compared with VEH group. a $P < 0.05$, aa $P < 0.01$ compared with 6-OHDA in combination with APO.

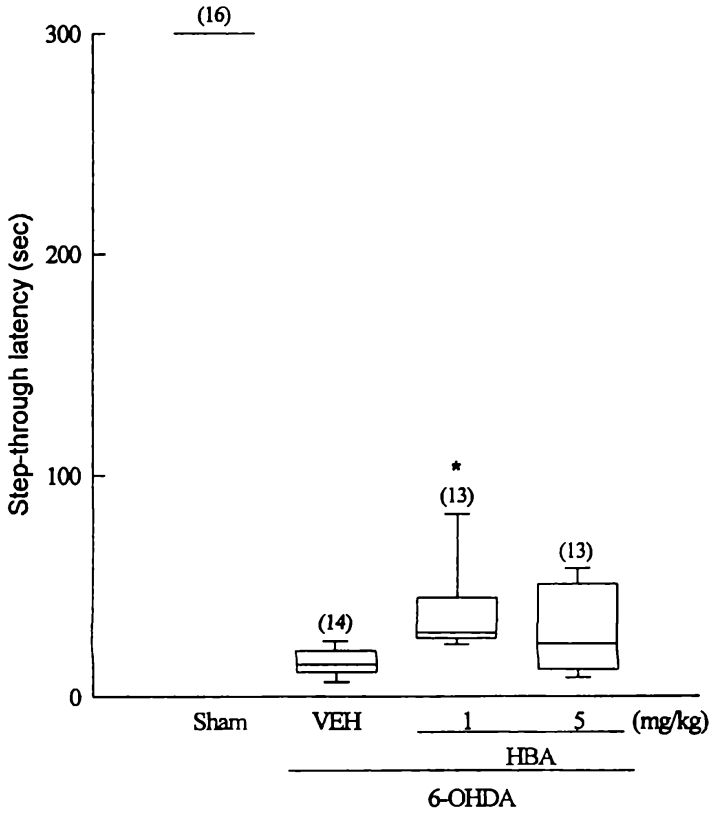

Fig. 5. Effect of *p*-hydroxybenzyl alcohol (HBA) on 6-hydroxydopamine (6-0HDA, i.c.v.) -induced impairment of avoidance in rats. Each column represents the median and range inside the 5th and 95th percentiles. * $P < 0.05$ compared with vehicle.

Table 1. Effects of *p*-Hydroxybenzyl Alcohol (HBA) and Piracetam (PIR) on the Step-through Latency of Non-shocked Rats After Apomorphine (APO) Administration

Drug	Dose (mg/kg, PO)	Step-through Latency (sec)	
		Training trial	Testing trial
Control		6.0 ± 0.4	8.9 ± 1.9
APO		8.2 ± 1.3	7.9 ± 1.1
HBA + APO	0.5	9.0 ± 1.2	8.2 ± 0.5
	1.0	9.2 ± 0.9	5.9 ± 0.9
	5.0	9.5 ± 1.2	6.2 ± 1.3
	25.0	10.5 ± 1.1	7.1 ± 0.6
PIR + APO	50	10.0 ± 1.9	7.7 ± 1.6
	100	10.3 ± 1.2	8.1 ± 2.0
	300	9.2 ± 0.9	7.4 ± 1.2

The results are expressed as mean ±.S.E. N = 8.

Table 2. Effects of *p*-Hydroxybenzyl Alcohol (HBA) in Combination with Various Drugs on the Step-through Latency of Non-shocked Rats After APO Administration

Drug (mg/kg)	Step-through Latency (sec)	
	Training trial	Testing trial
Control	6.0 ± 0.4	8.9 ± 1.9
APO	8.2 ± 1.3	7.9 ± 1.1
HBA 5.0 + APO	9.5 ± 1.2	6.2 ± 1.3
HBA 5.0 + APO + SKF 38393	13.2 ± 1.5	7.2 ± 0.7
APO + SCH 23390	11.7 ± 1.9	7.3 ± 1.1
HBA 5.0 + APO + SCH 23390	14.1 ± 2.2	7.3 ± 0.9
HBA 5.0 + APO + QUIN	12.2 ± 1.0	7.9 ± 1.2
APO + SUL	11.1 ± 1.7	6.8 ± 0.8
HBA 5.0 + APO + SUL	12.3 ± 2.7	7.0 ± 1.3

The results are expressed as mean I S.E. N = 8.

Effects of HBA and Other Drugs on Step-Through Latency of Unshocked Rats

HBA had no effect on the step-through latency of unshocked rats that were given APO in the training trial (Table 1). HBA in combination with other drugs also had no effect on the step-through latency of unshocked rats that were given APO (Table 2).

DISCUSSION

As is well known from the literature, the dopaminergic neuronal system plays an impor-

tant role in learning and memory.[8-9] Stimulation of the dopaminergic neuronal system is known to have a negative influence on learning and memory.[8-9] APO, a dopaminergic agonist, can significantly shorten step-through latency.[12] In the present study, APO also significantly shortened the step-through latency of the retention trial in the inhibitory avoidance task. Therefore, we demonstrated that the dopaminergic neuronal system plays a negative role in the inhibitory avoidance response. Piracetam, a nootropic, prolonged the step-through latency period that was previously shortened by APO. HBA also prolonged the step-through latency period previously shortened by APO in the inhibitory avoidance task, but the lower dosage (5 mg/kg) was more potent than the higher dosage (25 mg/kg). According to McGaugh's report, the dose-effect relationship of some cognitive activators was follows as inverted U curve, possible due to the peripheral nervous system and endocrine system.[21] On the other hand, several aspects argue against the possibility that the inhibitory avoidance response in drug-treated animals was related to motor alteration during training. In our earlier report, a high dose of HBA (25 mg/kg) selectively altered the motor activity and attention of animals in the inhibitory avoidance task.[4] However, the behavior of rats which received HBA or piracetam in the inhibitory avoidance task was grossly normal in the training and retention trials. The present data demonstrated that the attenuating effect of HBA on APO induced impairment of the inhibitory avoidance task was similar to earlier reports related to the memory processes.[1-4] The improvement brought about by HBA was more significant than brought about by piracetam.

D_1 and D_2 receptors play a modulatory role in learning and memory. Ichihara et al. reported that postsynaptic dopaminergic receptors are involved in the APO-induced impairment of the inhibitory avoidance response.[12] Recent studies have found that D_1 antagonists impaired the performance in various experimental tasks, and D_2 agonists impaired the performance in the inhibitory avoidance tasks.[10-11,14-15] Although the roles of D_1 and D_2 receptors in learning and memory appear distinct, some investigators have reported the role of dopaminergic receptors in learning and memory was dependent on the rodent strain, behavioral model and experimental design employed.[22-23] We further investigated the role of D_1 and D_2 receptors on the HBA-induced recovery from the APO-induced impairment of avoidance response. SKF 38393, a D_1-selective agonist, increased the activity of the dopaminergic neuronal system and significantly shortened the step-through latency in a retention trial.[14] The counteracting effect of HBA on APO-induced impairment of inhibitory avoidance response was inhibited by SKF 38393 at a dose which did not impair the avoidance. (±)-R-(+)-SCH 23390, a D_1 antagonist, facilitated the inhibitory avoidance response.[10-11] The dosage of R-(+)-SCH 23390 did not counteract the APO-induced impairment of the inhibitory avoidance response, but potentiated the effect of HBA. Therefore, a D_1 receptor antagonist counteracted the APO-induced impairment of avoidance, indicating that the counteracting effect of HBA on APO-induced impairment of inhibitory avoidance was partially related to D_1 receptors. (-)-Sulpiride, a selective D_2 antagonist, facilitated the inhibitory avoidance response.[10-11] The attenuating effect of HBA on the

APO-induced impairment was significantly potentiated by (-)-sulpiride at a dose which did not affect APO-induced impairment. Quinpirole, a selective D_2 agonist, impaired the inhibitory avoidance response.[14] The attenuating effect of HBA on APO-induced impairment was significantly blocked by quinpirole at a dose which did not impair the avoidance response. Some reports have shown that low doses of APO facilitated avoidance via presynaptic autoreceptors whereas high doses impaired the response via postsynaptic receptors.[12,24] Taking all these observations into consideration, we propose that both D_1 and D_2 receptor antagonists counteracted APO-induced impairment of the inhibitory avoidance response. We also suggest that the beneficial effect of HBA on APO-induced impairment of inhibitory avoidance response might be related to the dopaminergic neuronal system via postsynaptic D_1 and D_2 receptors.

Finally, the peripheral catecholaminergic system plays a modulatory role in learning and memory.[8,16] Some reports have suggested that peripheral antagonists or intravenous 6-OHDA blocked the effects of cognitive enhancers, and their facilitating effects were due to modulating peripheral catecholaminergic neuronal activity.[17] Intravenous 6-OHDA at 25 mg/kg did not impair the avoidance response, but blocked the counteracting effect of HBA on APO-induced impairment of avoidance. On the other hand, the central catecholaminergic system plays an important role in learning and memory.[8,18] Intracisternal 6-OHDA mainly decreases central catecholaminergic activities and impairs cognitive function.[19] Our present study showed that intracisternal 6-OHDA impaired the inhibitory avoidance response, and HBA at 1 and 5 mg/kg counteracted the effect of 6-OHDA. Therefore, we suggest that the counteracting effects of HBA on the inhibitory avoidance response might be related to modulation of peripheral and central catecholaminergic neuronal activities, consistent with the McGaugh's theory.[21] On the other hand, the report of Pan suggested that intracisternal 6-OHDA impairment of the avoidance response was partially due to decreasing central cholinergic activities.[19] Our previous report showed that the attenuating effect of HBA on drug-induced impairment of the inhibitory avoidance response was due to modulation of central adrenergic activity via the α_1-receptor but not to activation of the central cholinergic system.[3,4] In conclusion, the effects of HBA on APO-induced impairment of inhibitory avoidance response might be related to modulation of peripheral and central catecholaminergic neuronal activities via the α_1-receptor and postsynaptic D_1 and D_2 receptors.

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